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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,475	12/05/2003	Steve Pakola	113476.122US1	3082

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EXAMINER	
KIM, TAEYOON	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
10/16/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/729,475	PAKOLA ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-84* is/are pending in the application.

4a) Of the above claim(s) *62 and 73-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-61,63-72 and 80-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/18/07, 7/19/07, 7/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 57-84 are pending.

Response to Amendment

Applicant's amendment and response filed on Jul. 30, 2007 has been received and entered into the case.

Claims 1-56 are canceled, claims 62 and 73-79 are withdrawn from consideration as being drawn to non-elected subject matter, Claims 57-62, 63-72 and 80-84 have been considered on the merits. All arguments have been fully considered.

The claim rejection under 35 U.S.C.§112, 2nd paragraph, is withdrawn due to the amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g)

prior art under 35 U.S.C. 103(a).

Claims 57-61, 64-72 and 80-84 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Trese et al. (US 5,304,118; IDS reference) in view of Collen et al. (WO 2002/50290; IDS reference) in further view of Wu et al. (US 4,774,087; IDS reference).

Claims 57-61, 64-69, 71, 72 and 80-84 are drawn to a method of liquefying a vitreous and/or inducing posterior vitreous detachment of an eye of a subject, comprising contacting the vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin (claim 57); a limitation to the microplasmin being recombinant, stabilized, or stabilized and recombinant (claims 58, 67 and 81); a limitation to the composition being a liquid solution and the liquid composition being injected into the vitreous and/or the aqueous humor (claims 59, 68 and 82); a limitation to the subject being a human (claims 60, 69 and 83); a limitation to the method being used for treating a subject having a vitreoretinal disease or disorder (claim 61); a limitation to the method being performed as an adjunct to vitrectomy (claims 64 and 71); a limitation to the effective amount of microplasmin being in the range of 0.005 mg to 0.2 mg per eye (claims 65, 72 and 84); a method of treating a vitreoretinal disease or disorder of an eye of a subject, comprising contacting a vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin (claim 66); a method of performing a vitrectomy in a subject, comprising contacting a vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin, prior to or at the same time as the

removal of the vitreous (claim 80).

Trese et al. teach a method of inducing posterior vitreous detachment in a human eyes and treating certain medical disease and dysfunctions in the eye (column 1, lines 11-14) by injecting one to three units (effective amount) of plasmin during vitrectomy (see Abstract, Figure, and columns 1 and 2). Trese et al. also teach to use the method before surgical vitrectomy or simultaneously with the removal of the vitreous (vitrectomy) (see column 2, lines 26-32).

Trese et al. do not teach the use of microplasmin made recombinantly, stabilized, or stabilized and recombinantly.

Collen et al. teach mammalian plasminogen derivatives such as human microplasmin produced recombinantly and stabilization of such recombinant proteins (see Abstract; p.9, line 24).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to replace plasmin in the method of Trese et al. with microplasmin of Collen et al.

The skilled artisan would have been motivated to make such a modification because both plasmin and microplasmin share the same enzymatic activity as well known in the art, thus these are considered as art-recognized equivalents.

M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics

of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

Moreover, Wu et al. provide a motivation to use microplasmin over plasmin because of the advantage of the reduced size of microplasmin which does not require complexing and can act directly (see column 3, lines 34-37).

The person of ordinary skill in the art would have had a reasonable expectation of success in using microplasmin in the method of Trese et al. because the activity of microplasmin is well known to be equivalent to plasmin.

Although Trese et al. in view of Collen et al. in further view of Wu et al. do not particularly disclose the range of effective amount of microplasmin being 0.005 mg to 0.2 mg per eye. It would have been obvious for a person of ordinary skill in the art at the time of invention made to optimize the amount of microplasmin for the intended use of vitreolysis. The selection of effective amount of microplasmin would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that identification of the amount of microplasmin sufficient to induce posterior vitreous detachment or vitreolysis is critical to effectively treat the patients. A holding of

obviousness over the cited claims is therefore clearly required. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages. See *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382.; See also M.P.E.P. § 2144.05

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Claims 57, 63, 66 and 70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Trese et al. et al. (supra) in view of Collen et al. (supra) in further view of Wu et al. (supra) and Tanaka et al. (2000; IDS reference AX filed on Jan. 14, 2005).

Claims are drawn to a method of liquefying a vitreous and/or inducing posterior vitreous detachment of an eye of a subject, comprising contacting the vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin (claim 57); a limitation to the method being performed in the absence of vitrectomy (claims 63 and 70); a method of treating a vitreoretinal disease or disorder of an eye of a subject, comprising contacting a vitreous and/or an aqueous humor in the eye with an effective amount of a composition comprising microplasmin (claim 66).

Trese et al. in view of Collen et al. in further view of Wu et al. renders claims 57 and 66 obvious (see above).

Trese et al. in view of Collen et al. in further view of Wu et al. do not teach that

the method of claims 57 and 66 being performed in the absence of subsequent vitrectomy.

Tanaka et al. teach that pharmacological vitrectomy referring to the use of enzymes (e.g. microplasmin) in an effort to liquefy vitreous during or before performing vitreous surgery (vitrectomy). Tanaka et al. further teach the use of plasmin to make the vitreous surgery easier for better outcome or to avoid vitrectomy (see abstract).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use the method of Trese et al. in view of Collen et al. in further view of Wu et al. without additional/subsequent vitrectomy. The skilled artisan would have been motivated to make such a modification because Tanaka et al. teach that the use of pharmacological vitrectomy may allow avoiding subsequent vitrectomy.

The person of ordinary skill in the art would have had a reasonable expectation of success in using the method of Trese et al. in view of Collen et al. in further view of Wu et al. without further vitrectomy because effective amount of microplasmin would sufficiently achieve posterior vitreous detachment.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Response to Arguments

Applicant's arguments filed Jul. 30, 2007 have been fully considered but they are not persuasive.

Applicant argued by quoting Takeda vs. Alphapharm that in order to find a prima

facie case of unpatentability, a showing that 'the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required, and asserted that the examiner failed to show an objective teaching, suggestion, or motivation in the claim rejection made based on Trese et al. in view of Collen et al. in further view of Wu et al.

The examiner respectfully disagrees with the assertion because it has been clearly shown that Trese et al. teach the use of plasmin in a method of inducing posterior vitreous detachment in a human eye, and Collen et al. teach the use of microplasmin in the place of plasmin. The combination of the teaching by Collen et al. that microplasmin, a derivative of plasmin having the same enzymatic activity with plasmin, with the teaching of Trese et al. is obvious because Collen et al. teach that microplasmin would be an art-recognized equivalent to plasmin. It is well known in the art that microplasmin has the same catalytic domain as plasmin, thus having the same enzymatic activity, and according to Collen et al. it can replace plasmin for the same purpose. Thus, microplasmin is clearly an art-recognized equivalent to plasmin.

M.P.E.P. §2144.07 clearly states "The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when

heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)".

The examiner also provide a motivation to use microplasmin over plasmin based on the teaching provided by Wu et al. that there is an advantage of the reduced size of microplasmin which does not require complexing and can act directly.

According to the decision made by the Federal Circuit Court in DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641 (Fed. Cir. 2006), in order to make a *prima facie* case of obviousness, the suggestion and motivation to combine said references need not be explicitly stated in the text of the references. Rather, consideration of common knowledge and common sense when combining references is not only permitted *but required.* :

> ""Suggestion" test for obviousness does not require that suggestion, teaching, or motivation to combine cited prior art references be found in references themselves, or that such suggestion or motivation be explicitly stated; suggestion test is flexible rather than rigid and categorical, recognizing motivation to combine found in knowledge of persons of ordinary skill in art or nature of problem to be solved, as well as in references, and test not only permits, but requires, consideration of common knowledge and common sense."

See also the decision made by the US Supreme Court (KSR v. Teleflex 550 US82 USPQ2d 1385, 2007)

Therefore, the explicit motivation to combine the teaching of Trese et al. and Collen et.al. and/or Wu et al. is not required for obviousness rejection under 35

U.S.C.§103. Neverthelss, a person of ordinary skill in the art would recognize microplasmin as an successful alternative or equivalent to replace plasmin because it is a derivative of plasmin having the similar, if not identical, enzymatic activity as plasmin. Thus, the holding of obviousness rejection under 35 U.S.C.§103 is proper.

Applicant also argued that the intended use of microplasmin in Collen et al. and/or Wu et al. is not related to liquefy the vitreous, induce posterior vitreous detachment, treat vitreoretinal disease or disorders, or be used in a method of performing a non-pharmacological vitrectomy. This argument is not persuasive because the replacement of plasmin of Trese et al. with the microplasmin of Collen et al. and/or Wu et al. is not because the teaching of Collen et al. or Wu et al. that microplasmin is being used in treatment of strokes, rather, the replacement of plasmin with microplasmin is because a person of ordinary skill in the art would recognize microplasmin as an art-recognized equivalent to plasmin of Trese et al. Therefore, it would have been obvious to a person of ordinary skill in the art to replace plasmin with microplasmin of Collen et al. and/or Wu et al. the use of microplasmin in the method of Trese et al. Furthermore, since microplasmin is a derivative of plasmin and having the same activity as plasmin due to the same catalytic domain present in both, it is also considered to be suitable for the intended uses disclosed in the current invention.

Applicant argued in regard to the missing five Kringle domains in microplasmin and the importance of the Kringle domains in the substrate recognition. Since microplasmin taught by Collen et al. as well as Wu et al. retains the catalytic activity, a person of ordinary skill in the art would recognize microplasmin as an equivalent

substitute for plasmin. In the argument, applicant asserted that one of ordinary skill in the art would not think of microplasmin as a substitute for plasmin based on the fact that microplasmin lacks Kringle domains which involve in substrate recognition. However, Wu et al. teach that microplasmin demonstrated fibrinolytic activity at about the same level a molar basis as native plasmin (see column 3, lines 21-24). Based on such teachings from the prior art showing that microplasmin retains a catalytic activity, it would have been obvious to a person of ordinary skill in the art to substitute plasmin with microplasmin.

Applicant argued that there is no reasonable expectation of success in using microplasmin in the eye. Applicant is reminded that the substitution of plasmin with microplasmin as an art-recognized equivalent does not necessarily require expectation of success. M.P.E.P. §2144.07, which is the basis of the obviousness rejection in the previous office action, does not require motivation or expectation of success (see above). Considering the same activity found in microplasmin in comparison to plasmin as taught by Wu et al. (see above), it is reasonably expected that microplasmin would replace the activity of plasmin unless proven otherwise.

Further, applicant argued that Trese's own work suggests that it was not obvious to combine the art as proposed in the office action. It is not clear which teaching the applicant refers for this argument. Trese et al., the primary reference of the office action, does not disclose any teaching not to combine teaching of other art.

Finally, in regard to the teaching of Tanaka et al., applicant argued that Tanaka et al. do not suggest, or even hint at, using microplasmin as an alternative to plasmin.

The teaching of Tanaka et al. combined with the teachings of Trese et al. in view of Collen et al. in further view of Wu et al. is not whether Tanaka et al. teach the use of microplasmin in place of plasmin. As clearly discussed in the previous office action, the teaching of Tanaka et al. utilized was the use of pharmacological vitrectomy in combination with non-pharmacological, thus surgical, vitrectomy and the order of these two vitrectomy for the inducing posterior vitreous detachment.

Therefore, the holding of obviousness rejection under 35 U.S.C.§103 is proper.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is 571-272-9041. The examiner can normally be reached on 8:00 am - 4:30 pm ET (Mon-Fri).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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